CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-276

CORRESPONDENCE

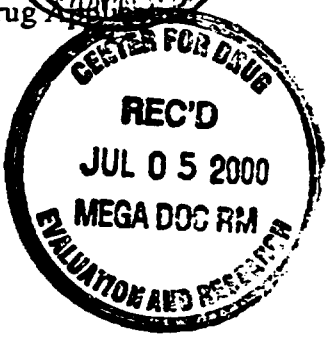
Pharmaceutical Research and Development
2800 Plymouth Road
Ann Arbor, MI
48105
Phone: (734) 622-7000

PARKE-DAVIS
A Warner-Lambert Division

June 30, 2000

NDA 21-276
Ref. No. 000
Estrostep® tablets

Re: Supplemental New Drug Application



Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
12229 Wilkins Avenue
Rockville, Maryland 20852

Dear Sir/Madam:

In accordance with Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21CFR 314.54, Parke-Davis, a Division of the Warner-Lambert Company, is submitting a supplemental New Drug Application for Estrostep®[a] tablets on behalf of and as agent for Parke-Davis Pharamceuticals, Limited. On June 19, 2000 the merger between Pfizer/Warner-Lambert was completed. The information contained in this supplemental NDA was conducted by Parke-Davis, thus all research reports contained in this submission retain the Parke-Davis name. This supplement provides evidence for a new indication of use for the approved and marketed Estrostep for *treatment of moderate acne vulgaris in females between* [redacted] *and 49 years of age, who have no known contraindication to oral contraceptive therapy, desire contraception, have achieved menarche, and are unresponsive to topical anti-acne medications.*

The administrative number for this supplement (21-276) for Estrostep for the treatment of acne was preassigned to this application on May 24, 2000. It is our understanding that this administrative number will become non-existent upon approval of the submission and all subsequent references will be made to the original NDA number, NDA 20-130 for Estrostep tablets.

As required under the Prescription Drug User Fee Act, the application fee of [redacted] has been sent to the Food and Drug Adminstration in care of Mellon Bank, Pittsburgh, Pennsylvania on June 19, 2000. The User Fee Identification Number for this submission is 3960. A copy of the User Fee Cover Sheet, Form FDA 3397, for this payment is contained under Item 18.

Estrostep, an oral contraceptive, has been investigated by Parke-Davis under [redacted] in the Division of Reproductive and Urologic Drug Products. The NDA 20-130 for Estrostep tablets was approved on October 9, 1996, for oral contraception. Estrostep is provided as a 21-day package with continuous dosage regimen consisting of 21 oral contraceptive tablets or as Estrostep® Fe, a 28-day package with continuous dosage regimen consisting of 21 oral contraceptive tablets and 7 ferrous fumarate tablets.

[a] Estrostep tablets is a trademark of Warner-Lambert, its affiliates, and subsidiaries.

Estrostep has been investigated under [redacted] under the auspices of the Division of Dermatologic and Dental Drug Products (DDDDP) submitted April 22, 1998, for the treatment of moderate acne vulgaris. During development of Estrostep for the treatment of acne, 2 formal meetings were conducted between Parke-Davis and the DDDDP. A summary of these meetings and the agreements reached can be found in Item 3.2 with the formal meeting minutes immediately following.

The human pharmacokinetic data, in adults, and non-clinical pharmacology and toxicology for ethinyl estradiol and norethindrone is cross-referenced to NDA 20-130. Reference is also made to our skin aging [redacted] for femhrt, our approved NDAs 17-876, 17-875, 17-354 and 17-355 for Loestrin®, [redacted] and for our approved NDA 21-065 for femhrt® 1/5, all of which contain the same active drug substances, ethinyl estradiol and norethindrone acetate, albeit in different dosages.

This supplement in its entirety is being provided in accordance with the January 1999 Guidances for Industry entitled *Providing Regulatory Submissions in Electronic Format – NDAs* (Jan 1999) and *Providing Regulatory Submission in Electronic Format – General Considerations* (Jan 1999). The archival copy is provided in electronic format. All documents that require original signatures are provided as a paper archive copy. In accordance with the same Guidances and as requested by the Division, we are providing a paper review copy. At the request of Ms. Olga Cintron, Project Manager of DDDDP, on May 24, 2000, 8 copies of Volume 1 are also provided as desk/paper review copies. To facilitate quality assurance and flexibility in reviewing from electronic to paper versions: 1) most paper volume page numbers are present in the upper right-hand corner of documents, and 2) most item and volume numbers are located in the lower right-hand corner of documents.

Reference is also made to our Electronic Regulatory Submission Plan (submitted under [redacted] Attachment A) that describes the exceptions to the FDA guidances, which was reviewed by Dr. Randy Levin (Director, Information Technology Office) and approved with minor modifications on November 18, 1999. Additional reference is made to our letter of March 13, 2000 [redacted] which responded to and provided clarifications to the recommendations for data transfer to the Division of Biometrics (Attachment B).

The electronic files for this submission are contained on 1 CD-ROM totaling ~584MB. All electronic files have been scanned with Network Associates VirusScanNT Version 4.0.3.a. Some PDF files contain extra non-paginated cover pages so that the electronic files and paper copies are identical.

As suggested in the *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application* (July 1988), we are providing SAS programs used to generate the results. The SAS programs are stored in Item 11 [redacted] An explanation of the SAS programs can be found in the document called SAS Program Directory.pdf (stored in the /Programs/folder).

NDA Item 13 Patent Information, Item 16 Debarment Certification, Item 18 User-Fee Cover Sheet, Item 19 Financial Disclosure, and Item 20 the Request for Pediatric Waiver, are all contained in Volume 1 of this submission. Please refer to the attached Form FDA 356h and the NDA Index, which detail the complete contents of the supplement.

The chemistry, manufacturing and controls information for Estrostep tablets is submitted by cross-reference to NDA 20-130. Clinical studies were conducted with approved market-image Estrostep tablets. This supplement does not propose any changes in the formulation, dosage forms, manufacturing procedures, recommended dosages, or dosing regimen for Estrostep tablets. Our Request for Exclusion from Environmental Assessment for the active substances is provided in Item 4 and cross-references NDA 21-065 for femhrt and NDA 17-354, 17-355, 17-875, and 17-876 for Loestrin. Pursuant to 21 CRF 314.440, a complete copy of the Chemistry, Manufacturing and Controls section (Item 4) of this supplement has been sent to the FDA District Offices in Newark, New Jersey and San Juan, Puerto Rico. Field Copy Certification is provided in Item 17.

Copies of all DMF letters referenced in this supplement are located in the Chemistry, Manufacturing and Controls section (Item 4) as well as provided immediately following this cover letter (Attachment C).

For any questions regarding this submission during the NDA review, please contact either myself at 734-622-5000 or Dr. Joanna Hinton at 734-622-2346 or send a facsimile to either of us at 734-622-3283.

Sincerely,

Mary E. Taylor, MPH
Senior Director
Worldwide Regulatory Affairs

MET/kb
06-30-2000\RN-000\21-276\CI-0376\Letter

NDA Copies: "Blue" Archive, Vol.1 includes Electronic Archive Copy (1-CD)
"Red" Chemistry, Vol. 1-4
"Orange" Biopharmaceutics, Vol. 1-3, 8-11
"Tan" Medical, Vol. 1-3, 12-30
"Green" Biometrics, Vol. 1-3, 31-49
"Maroon" Field (Newark), Vol. 1-4
"Maroon" Field (San Juan), Vol. 1-4
Desk Copies (8), Vol. 1-3

Pharmaceutical Research and Development
2800 Plymouth Road
Ann Arbor, MI
48105
Phone (734) 622-7000

PARKE-DAVIS
A Warner-Lambert Division

August 29, 2000

sNDA 21-276
Estrostep® Tablets

Re: Desk Copies

Ms. Olga Cintron
Project Manager
Division of Dermatologic and
Dental Drug Products (HFD-540)
Document Control Room N248
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

Dear Ms. Cintron:

Reference is made to sNDA 21-276 for Estrostep®[a] tablets and to your telephone request of August 21, 2000, in which you asked to receive 1 paper desk copy of those volumes within Item 8 that contain protocols 376-403 and 376-404. Please find enclosed:

sNDA 21-276, Item 8 Vol 12	Protocol 376-403 begins on page 85; it is Appendix A.2 of RR 720-04342
sNDA 21-276, Item 8 Vol 16	Protocol 376-404 begins on page 69; it is Appendix A.2 of RR 720-04420

Should you have any questions or comments regarding this submission, please contact me at 734/622-2346 or send a facsimile to 734/622-3283.

Sincerely,

Joanna Hinton, Ph.D.
Senior Manager
Worldwide Regulatory Affairs

JH/kb
08-29-2000\21-276\C1-0376\Letter
Attachments

[a] Estrostep is a registered trademark of Warner-Lambert, its affiliates, and subsidiaires.

Pharmaceutical Research and Development
2800 Plymouth Road
Ann Arbor, MI
48105
Phone (734) 622-7000

PARKE-DAVIS
A Warner-Lambert Division

September 6, 2000

sNDA 21-276
Ref. No. 001
Estrostep®[a] Tablets

Re: General Correspondence

Ms. Olga Cintron
Project Manager
Division of Dermatologic and
Dental Drug Products (HFD-540)
Document Control Room N248
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, Maryland 20850

NEW CORRESP
NC

Dear Ms. Cintron:

Reference is made to sNDA 21-276. Reference is also made to our phone contacts of August 16-21, 2000, in which we arranged to hold a teleconference to discuss 3 electronic format questions about the submission.

We agreed to hold a teleconference on Thursday September 7, 2000 from 1:30 to 2:00 p.m. Please call us at 1:30 p.m. in my office at 734/622-2346. We will have the electronic sNDA available on a computer to help us navigate and most efficiently respond to your questions.

Here is a list of probable Pfizer attendees for the teleconference:

Melissa Yeh, Scientific Information Engineering, Project Leader
Pauline Kim, Scientific Information Engineering, Dev. Manager
Jacqueline Jackson, Regulatory Affairs, Submissions Coordinator
Bonnie Mitchell, Clinical, Contract Project Manager
Mary Flack, M.D., Clinical Research, Director
Joanna Hinton, Ph.D., Regulatory Affairs, FDA Liaison

We will be prepared to discuss the 3 questions you posed on August 16, 2000 as well as other electronic questions.

1) Unable to locate a Master Index that would outline the contents of each file and folder. Would we be able to provide one?
2) Unable to locate the line listings for the clinical studies (outcomes on per patient basis). They would like to see line listings.
3) Unable to locate Annotated CRFs.

[a] Estrostep is a registered trademark of Warner-Lambert Company, its affiliates, and subsidiaries.

Should you have any questions regarding this submission, please feel free to contact me at 734/622-2346 or send a facsimile to 734/622-3283.

Sincerely,

Joanna Hinton, Ph.D.
Senior Manager
Worldwide Regulatory Affairs

JH/kb
09-06-2000\RN-001\21-276\CI-0376

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-276

SEP 7 2000

Park-Davis Pharmaceutical Research
Attention: Mary E. Taylor, MPH
Senior Director, Worldwide Regulatory Affairs
2800 Plymouth Road
PO Box 1047
Ann Arbor, Michigan 48106-1047

Dear Ms. Taylor:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Estrostep (norethindrone acetate/ethinyl estradiol) Tablets

Review Priority Classification: Standard (S)

Date of Application: June 30, 2000

Date of Receipt: July 3, 2000

Our Reference Number: NDA 21-276

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 1, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be May 3, 2001 and the secondary user fee goal date will be July 3, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
Attention5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic and Dental Drug Products, HFD-540
Attention9201 Corporate Blvd.
Rockville, Maryland 20850-3202

If you have any questions, call Olga I. Cintron, R.Ph., Project Manager, at (301) 827-2020.

Sincerely,

/S/

Mary Jean Kozma-Fornaro 9/7/00
Supervisor, Project Management Staff
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Archival NDA 21-276
HFD-540/Div. Files
HFD-540/O.Cintron

DISTRICT OFFICE

Drafted by: smc/September 7, 2000

ACKNOWLEDGEMENT (AC)

Pharmaceutical Research and Development
2800 Plymouth Road
Ann Arbor, MI
48105
Phone (734) 622-7000

PARKE-DAVIS
A Warner-Lambert Division

September 14, 2000

sNDA 21-276
Ref. No. 002
Estrostep® Tablets

Re: Amendment, Response to FDA Request for Information

NEW CORRESP
NC

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Document Control Room N214
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Wilkin:

Reference is made to sNDA 21-276 for Estrostep® Tablets. Reference is also made to FDA – Pfizer teleconference on September 7, 2000, which we discussed several electronic format questions and provided assistance with navigating the electronic submission. During that meeting we agreed to provide a paper Master Table of Contents to facilitate review.

Please find enclosed the Master Table of Contents as Attachment 1. For ease of review, volume and page numbers in the Master Table of Contents appear on the lower and upper right corner of the submission, respectively.

Also enclosed as Attachment 2 is our summary of the September 7, 2000 teleconference.

If you should have questions regarding this submission please feel free to contact me at 734/622-2346 or send a facsimile to 734/622-3283.

Sincerely,

Joanna Hinton, Ph.D.
Senior Manager
Worldwide Regulatory Affairs

Desk Copy: Olga Cintron (HFD-540)

JH/kb
09-14-2000\RN-002\21-276\CI-0376\Letter
Attachments

Pharmaceutical Research and Development
2800 Plymouth Road
Ann Arbor, MI
48105
Phone: (734) 622-7000

PARKE-DAVIS
A Warner-Lambert Division

October 9, 2000

NDA ORIG AMENDMENT

sNDA 21-276
Ref. No. 003
Estrostep® (norethindrone acetate/ethinyl estradiol) Tablets

Re: Response to FDA Request for Information

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Document Control Room N214
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

BM

Dear Dr. Wilkin:

Reference is made to our pending sNDA 21-276 for Estrostep®[a] (norethindrone acetate/ethinyl estradiol) tablets submitted on June 30, 2000 (Ref. No. 000). Reference is also made to a telephone conversation with Ms. Olga Cintron, of your Division, and myself on August 21, 2000. Ms. Cintron indicated that DDMAC reviewers "were unable to locate the evidence of validation or performance within a clinical trial setting" of the Acne-Specific Quality of Life (QoL) instrument used. She asked that we provide DDMAC (attention to Iris Masucci) with the location of this information or provide them with relevant supporting references. This submission is the response to that request for information.

This response in its entirety is being provided in accordance with the January 1999 Guidances for Industry entitled, *Providing Regulatory Submissions in Electronic Format – NDAs* and *Providing Regulatory Submissions in Electronic Format – General Considerations*. The archival copy is provided in electronic format. All documents that require original signatures are provided as a paper archive copy. In accordance with the same Guidances, we are providing a paper review copy.

The electronic files are contained on 1 CD-ROM using approximately 1.66 MB. All electronic files have been scanned with Network Associates VirusScanNT Version 4.0.3a with Virus Definitions 4.0.4098.

[a] Estrostep is a registered trademark of Warner-Lambert Company, its affiliates, and subsidiaries.

ORIGINAL

Should you have any comments or questions regarding these materials or this information, please contact me at 734/622-2346 or John Kirk at 734/622-7783 or send a facsimile to 734/622-3283.

Sincerely,

Joanna P. Hinton, Ph.D.
Senior Manager
Worldwide Regulatory Affairs

Desk Copy: Iris Masucci, Pharm. D. (HFD-042)
Jennifer Mercier (HFD-580)
Olga Cintron (HFD-540)

JH/kb
10-09-2000\RN-003\21-276\CI-0376\Letter
Attachment

Pharmaceutical Research and Development
2800 Plymouth Road
Ann Arbor, MI
48105
Phone: (734) 622-7000

PARKE-DAVIS
A Warner-Lambert Division

November 7, 2000

sNDA 21-276
Ref. No. 004
Estrostep® (norethindrone acetate/ethinyl estradiol) Tablets

Re: Response to FDA Request for Information

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products (HFD-540)
Document Control Room N214
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

ARCHIVE COPY
Bm

Dear Dr. Wilkin:

Reference is made to our pending sNDA 21-276 for Estrostep®[a] (norethindrone acetate/ethinyl estradiol) tablets submitted on June 30, 2000 (Ref. No. 000). Reference is also made to a fax received on October 25, 2000, from Ms. Olga Cintron of your Division that contained 18 questions from the Medical Officer. This correspondence provides an initial response to that request for information.

Attached, in the Notes to Reviewer, are responses to 10 of the 18 questions (Questions 1, 2, 5, 8, 9, 12, 13, 14, 15, and 16) from the October 25, 2000 fax. Responses to the remaining 8 questions (3, 4, 6, 7, 10, 11,17, and 18) will be provided in a forthcoming submission as these questions required additional programming analysis. The Table of Contents for the Case Report Forms is also attached. The actual CRFs will be provided in the electronic response.

To expedite our response to your request, we are providing this initial response as a hardcopy by sending this fax. It will be followed shortly by an electronic submission. The electronic response will be made in accordance with the January 1999 Guidances for Industry entitled, *Providing Regulatory Submissions in Electronic Format – NDAs* and *Providing Regulatory Submissions in Electronic Format – General Considerations*.

[a] Estrostep is a registered trademark of Warner-Lambert Company, its affiliates, and subsidiaries.

Should you have any questions regarding this submission, please contact me at 734/622-2346 or John Kirk at 734/622-7783, or send a facsimile to 734/622-3283.

Sincerely,

Joanna Hinton, Ph.D.
Senior Manager
Worldwide Regulatory Affairs

JH/kb
11-07-2000\RN-004\21-276\CI-0376\Letter
Attachments

Pharmaceutical Research
2800 Plymouth Road Phone: (734) 622-7000
Ann Arbor, MI
48105

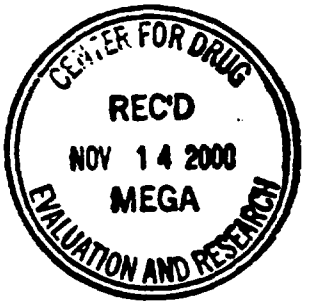
PARKE-DAVIS

November 10, 2000

sNDA 21-276 NDA ORIG AMENDMENT
Ref. No. 005
Estrostep® (norethindrone acetate/ethinyl estradiol) Tablets

Re: Response to FDA Request for Information

BM



Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Document Control Room N214
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Wilkin:

Reference is made to our pending sNDA 21-276 for Estrostep®[a] (norethindrone acetate/ethinyl estradiol) tablets submitted on June 30, 2000 (Ref. No. 000). Reference is also made to a fax received on October 25, 2000, from Ms. Olga Cintron of your Division that contained 18 questions from the Medical Officer. This correspondence provides an initial response to that request for information.

Attached, in the Item 8 Notes to Reviewers, are responses to 10 of the 18 questions (Questions 1, 2, 5, 8, 9, 12, 13, 14, 15, and 16) from the October 25, 2000 fax. Responses to the remaining 8 questions (3, 4, 6, 7, 10, 11, 17, and 18) will be provided in a forthcoming submission as these questions required additional programming analysis.

To expedite our response to your request, we previously faxed (November 7, 2000) and sent (November 8, 2000, Ref. No. 004) a hardcopy of the Notes to Reviewers. This response in its entirety is being provided in accordance with the January 1999 Guidances for Industry entitled, *Providing Regulatory Submissions in Electronic Format – NDAs* and *Providing Regulatory Submissions in Electronic Format – General Considerations*. The archival copy is provided in electronic format. All documents that require original signatures are provided as a paper archive copy. In accordance with the same Guidances, we are providing a paper review copy.

ORIGINAL

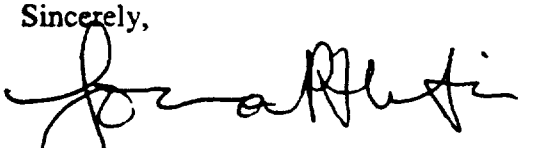
[a] Estrostep is a registered trademark of Warner-Lambert Company, its affiliates, and subsidiaries.

The electronic files are contained on 1 CD-ROM using approximately 362.3 MB. All electronic files have been scanned with Network Associates VirusScanNT Version 4.0.3a with Virus Definitions 4.0.4103. The electronic archive contains the following:

- Cover Letter
- FDA Form 356h
- Item 1 Table of Contents
- Item 8, Table of Contents
- Item 8, Notes to Reviewers (Response to Questions)
- Item 12, Table of Contents
- Item 12, Requested Case Report Forms

If you have any questions regarding this submission please contact me at 734/622-2346 or John Kirk at 734/622-7783, or send a facsimile to 734/622-3283.

Sincerely,



Joanna Hinton, Ph.D.
Senior Manager
Worldwide Regulatory Affairs

Desk Copy: Olga Cintron (HFD-540)

JH/kb
11-10-2000\RN-005\21-276\CI-0376\Letter
Attachments

Pharmaceutical Research
2800 Plymouth Road Phone: (734) 622-7000
Ann Arbor, MI
48105

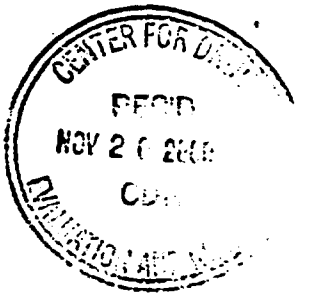
NDA GRID ASSIGNMENT

PARKE-DAVIS

November 17, 2000

sNDA 21-276
Ref. No. 006
Estrostep® (norethindrone acetate/ethinyl estradiol) Tablets

Re: 4-Month Safety Update



Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products (HFD-540)
Document Control Room N214
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Wilkin:

Pursuant to 21 CFR 314.50(d)(5)(vi), enclosed is the Four-Month Safety Update for the supplemental New Drug Application 21-276 for Estrostep®[a] (norethindrone acetate and ethinyl estradiol) submitted on June 30, 2000 (Ref. No. 000), and received by the Agency on July 3, 2000. This supplement provides evidence for a new indication of use for the approved and marketed Estrostep: *treatment of moderate acne vulgaris in females between □ and 49 years of age, who have no known contraindication to oral contraceptive therapy, desire contraception, have achieved menarche, and are unresponsive to topical anti-acne medications.* Included in the sNDA were 2 completed clinical trials (376-403 & 376-404). Inclusive safety data from these completed trials were summarized in the Integrated Summary of Safety (ISS) (RR-REG 720-04389).

Reference is also made to a telephone conversation between Ms. Olga Cintron and Dr. Marty Okun of your Division and myself on August 16, 2000. Dr. Okun requested that we provide a summary of the post-marketing experiences with Estrostep as an oral contraceptive. It was suggested this information be included with the 4-Month Safety Update.

This submission therefore includes 2 items:

1. The 4-Month Safety Update Report. This report summarizes the follow-up of the one pregnancy that occurred in an Estrostep-treated subject during the conduct of Studies 376-403 and –404. There were no post-sNDA nor any ongoing Parke-Davis nor Pfizer-sponsored Estrostep clinical trials. Consequently, there is no other new safety information which would affect the conclusions or labeling as contained in the original sNDA; and

2. A Review of Estrostep Post-Marketing Safety Data (period covered October 9, 1996 through August 31, 2000).

---

[a] Estrostep is a registered trademark of Warner-Lambert Company, its affiliates, and subsidiaries.

ORIGINAL

Finally, reference is made to a telephone conversation between Ms. Olga Cintron of your Division and myself on October 30, 2000. During this conversation Ms. Cintron indicated that it was preferable to submit both items of this 4-month safety update together provided a delay of not more than 2-3 weeks occurred from the submission deadline.

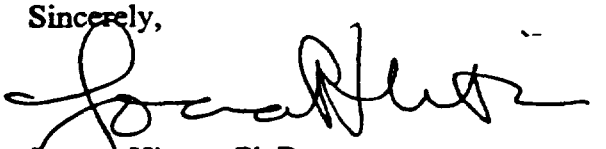
This response in its entirety is being provided in accordance with the January 1999 Guidances for Industry entitled, *Providing Regulatory Submissions in Electronic Format – NDAs* and *Providing Regulatory Submissions in Electronic Format – General Considerations*. The archival copy is provided in electronic format. All documents that require original signatures are provided as a paper archive copy. In accordance with the same Guidances, we are providing a paper review copy.

The electronic files are contained on 1 CD-ROM using approximately 8.5 MB. All electronic files have been scanned with Network Associates VirusScanNT Version 4.0.3a with Virus Definitions 4.0.4103. The electronic archive contains the following:

- Cover Letter
- FDA Form 356h
- Item 1 Table of Contents
- Item 9, Safety Update, Table of Contents
- Item 9, 4-Month Safety Update Report, RR-REG 720-30050
- Item 9, A Review of Estrostep Post-Marketing Safety
- Item 9, Publications

If there are any questions, please feel free to contact me at 734/622-2346 or Mr. John Kirk at 734/622-7783, or send a facsimile to 734/622-3283.

Sincerely,



Joanna Hinton, Ph.D.
Senior Manager
Worldwide Regulatory Affairs

Desk Copy: Jennifer Mercier (HFD-580 – Paper Desk Copy)
Olga Cintron (HFD-540 – Paper Desk Copy)

JH/kb 11-17-2000\RN-006\21-276\CI-0376\Letter
Attachments

Pharmaceutical Research
2800 Plymouth Road Phone: (734) 622-7000
Ann Arbor, MI
48105

PARKE-DAVIS

December 20, 2000

sNDA 21-276
Ref. No. 008
Estrostep® (norethindrone acetate/ethinyl estradiol) Tablets

Re: Response to FDA Request for Information

Dr. Jose Carreras
Division of Scientific Investigations (HFD-45)
Center for Drug Evaluation and Research
Document Control Room 125
Food and Drug Administration
Metro Park North
7520 Standish Place
Rockville, Maryland 20855

Dear Dr. Carreras:

Reference is made to our pending sNDA 21-276 for Estrostep®[a] (norethindrone acetate/ethinyl estradiol) tablets submitted on June 30, 2000 (Ref. No. 000) for the use of Estrostep in the treatment of moderate acne vulgaris. Reference is also made to a telephone conversation we had on November 11, 2000, and an email I received from you on November 27, 2000, which requested information on 3 different clinical sites. This correspondence provides the information as you requested.

Attached please find 3 volumes; one for each of the requested sites: Jones 404-001; Warren 404-010; and Hamlin 404-014. Each binder contains the following site-relevant information as requested:

- Protocol 376-404 and amendments
- Primary Endpoints data listing
- Listing of All Adverse Events
- Listing of Subjects' Early Terminations
- Copies of 4 randomly selected subjects' completed CRFs (blinded random number draw)

The information provided herein is also available in the original electronic archive of sNDA 21-276, albeit in integrated study 376-404 listings.

As we agreed to, I am copying Ms. Olga Cintron of the Division of Dermatologic and Dental Drug Products on this letter so she is aware of our communication. Furthermore, reference is made to a telephone conversation between myself and Ms. Cintron on December 11, 2000. Ms. Cintron indicated that I did not need to submit copies of the 3 volumes you requested to the sNDA file. However, she recommended that I should submit an electronic archive copy of the cover letter since sNDA 21-276 was originally

[a] Estrostep is a registered trademark of Warner-Lambert Company, its affiliates, and subsidiaries.

submitted in accordance with the January 1999 Guidances for Industry entitled, *Providing Regulatory Submissions in Electronic Format – NDAs* and *Providing Regulatory Submissions in Electronic Format – General Considerations.* Consequently, an electronic archive copy of the cover letter and the 356h form are being submitted only to the Central Document Room. The electronic files are contained on 1 CD-ROM using approximately 270 KB. All electronic files have been scanned with Network Associates VirusScanNT Version 4.0.3a with Virus Definitions 4.0.4103.

Furthermore, corresponding paper copies of the cover letter and 356h form are being provided to Dr. Jonathan Wilkin and Ms. Olga Cintron both of the Division of Dermatologic and Dental Drug Products.

If you have any questions regarding this submission please contact me at 734/622-2346 or John Kirk at 734/622-7783, or send a facsimile to 734/622-3283.

Sincerely,

Joanna Hinton, Ph.D.
Senior Manager
Worldwide Regulatory Affairs

Cover letter and copy of 356h (paper): Olga Cintron (HFD-540)
Cover letter and copy of 356h (paper): Jonathan Wilkin, M.D. (HFD-540)
Cover letter and 356h (electronic & paper): Central Document Room

JH/kb
12-20-2000\RN-008\21-276\CI-0376\Letter

Attachments: 3 Paper Volumes:
404-001
404-010
404-014

Pharmaceutical Research
2800 Plymouth Road Phone (734) 622-7000
Ann Arbor, MI
48105

BM

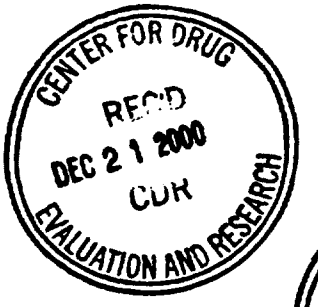
PARKE-DAVIS

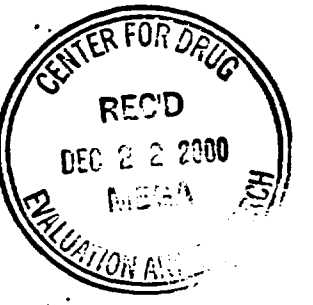
December 20, 2000

sNDA 21-276
Ref. No. 007
Estrostep® (norethindrone acetate/ethinyl estradiol) Tablets

Re: Response to FDA Request for Information; Amended Reports

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Document Control Room N214
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850





Dear Dr. Wilkin:

Reference is made to our pending sNDA 21-276 for Estrostep®[a] (norethindrone acetate/ethinyl estradiol) tablets submitted on June 30, 2000 (Ref. No. 000). Reference is also made to a fax received on October 25, 2000, from Ms. Olga Cintron of your Division that contained 18 questions from the Medical Officer. This correspondence provides the full response to that request for information. Reference is also made to an additional fax received on December 4, 2000, from Ms. Olga Cintron of your Division that contained 2 questions from the Medical Officer requesting further clarification about "early terminations." Responses to these 2 questions are also provided.

Complete responses to all 18 questions from the Medical Officer (fax 10-25-00) and 2 additional questions (fax 12-4-00) are located in Item 8, Other Folder. Previously, responses to Questions 1, 2, 5, 8, 9, 12, 13, 14, 15, and 16 were provided on November 7, 2000 [Ref. No. 004 (paper)] and on November 10, 2000 [Ref. No. 005 (paper & electronic)]. Responses to these 10 questions have not changed. In prior agreement with the Division, duplicate copies of the previously provided CRFs are not included in this correspondence.

Reference is also made to 2 emails sent to Ms. Olga Cintron of your Division by myself. The first on December 11, 2000, which provided a partial response to the questions received in the December 4, 2000 fax. The second on December 15, 2000, which provided a pdf file that contained our complete responses to all 18 questions from the fax of October 25, 2000 and 2 questions from the fax December 4, 2000. The response document included herein Item 8, Other Folder is identical to that provided in the December 15, 2000 email.

[a] Estrostep is a registered trademark of Warner-Lambert Company, its affiliates, and subsidiaries.

ORIGINAL

Also included in this correspondence within Item 8 are revised copies of the Study 376-404 report and the Integrated Summary of Safety (ISS). An incorrect weight value for study 376-404, Appendix C.38: Weight / Body Mass Index, All Randomized Subjects has been corrected. An incorrect weight value for the ISS, Appendix C.24 Weight / Body Mass Index, All Randomized Subjects has also been corrected. The revisions to these reports are minor and do not impact on study conclusions. Although the corrections comprise only 2 revised pages per report, the entire reports are provided to ensure you have the most up-to-date, complete and accurate versions. Please note that the references for the ISS are not provided in this submission. Please refer to the original June 30, 2000 electronic archive submission.

This response in its entirety is being provided in accordance with the January 1999 Guidances for Industry entitled, *Providing Regulatory Submissions in Electronic Format – NDAs* and *Providing Regulatory Submissions in Electronic Format – General Considerations*. The archival copy is provided in electronic format. All documents that require original signatures are provided as a paper archive copy. In accordance with the same Guidances, we are providing a paper review copy.

The electronic files are contained on 1 CD-ROM using approximately 9.95 MB. All electronic files have been scanned with Network Associates VirusScanNT Version 4.0.3a with Virus Definitions 4.0.4109. The electronic archive contains the following:

- Cover Letter
- FDA Form 356h
- Item 1 Table of Contents
- Item 8, Table of Contents
- Item 8, Notes to Reviewers
- Item 8, Other Folder (Response to 10-25-00 FAX and 12-04-00 FAX)
- Item 8, Acne Folder (Study 404 Report)
- Item 8, ISS Folder (ISS)

To facilitate quality assurance and flexibility in reviewing from electronic to paper versions, please note the following: 1) The paper review copy consists of 6 volumes. 2) Volumes are indicated on the binder labels (x of 6). 3) Page numbers will run consecutively and be located on the top right corner. 4) Item number designation is located on the lower right corner.

If you have any questions regarding this submission please contact me at 734/622-2346 or John Kirk at 734/622-7783, or send a facsimile to 734/622-3283.

Sincerely,

Joanna Hinton, Ph.D.
Senior Manager
Worldwide Regulatory Affairs

Desk Copy: Olga Cintron (HFD-540)

JH/kb
12-20-2000\RN-007\21-276\CI-0376\Letter

Attachments
1 CD: Volumes 1-6 (Central Document Room)
Volume 1: Item 1 Table of Contents and Item 8 Table of Contents, Notes to Reviewer, and Response to 10-25-00 FAX and 12-04-00 FAX.
Volumes 2-5: Item 8, Study 376-404 Report
Volume 6: Item 8, ISS report

Pharmaceutical Research and Development
2800 Plymouth Road
Ann Arbor, MI
48105
Phone: (734) 622-7000

PARKE-DAVIS
A Warner-Lambert Division

January 30, 2001

sNDA 21-276
Ref. No. 009
Estrostep® (norethindrone acetate/ethinyl estradiol) Tablets

Re: Amendment to Pending Application

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products (HFD-540)
Document Control Room N214
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

NDA AMENDMENT
BM

Dear Dr. Wilkin:

Reference is made to our pending sNDA 21-276 for Estrostep®[a] (norethindrone acetate/ethinyl estradiol) tablets submitted on June 30, 2000 (Ref. No. 000) for the use of Estrostep in the treatment of moderate acne vulgaris. Reference is also made to a telephone conversation with Ms. Olga Cintron, of your Division, and myself on August 21, 2000. Ms. Cintron indicated that DDMAC reviewers "were unable to locate the evidence of validation or performance within a clinical trial setting" of the Acne-Specific Quality of Life (QoL) instrument used. She asked that we provide DDMAC (attention to Iris Masucci) with the location of this information or provide them with relevant supporting references. Reference is also made to our October 9, 2000 submission, which provided the response to the August 21, 2000 request for information.

This correspondence provides an additional report that supports the Acne-Specific QoL instrument validation.

Since our October 9, 2000 response, a new report summarizing the psychometric soundness and responsiveness of the Acne-Specific QoL instrument has been finalized. We believe that this additional information of the Acne- Specific QoL could be of interest to DDMAC during the review of the sNDA 21-276 for Estrostep. The inclusion of the Acne-Specific QoL in two identical, randomized, double-blind, placebo-controlled trials designed to assess the effect of Estrostep on facial acne presented opportunities to not only measure changes in quality of life attributable to Estrostep, but also to confirm and extend the previous psychometric evaluation of the Acne-QoL. Consequently, as a matter of scientific rigor and completeness and consistent with the ERIQA (2000) guidelines, psychometric soundness and responsiveness of the Acne-Specific QoL instrument was established. The attached report describes the results of these psychometric analyses.

[a] Estrostep is a registered trademark of Warner-Lambert Company, its affiliates, and subsidiaries.

ORIGINAL

This response in its entirety is being provided in accordance with the January 1999 Guidances for Industry entitled, *Providing Regulatory Submissions in Electronic Format – NDAs* and *Providing Regulatory Submissions in Electronic Format – General Considerations*. The archival copy is provided in electronic format. All documents that require original signatures are provided as a paper archive copy. In accordance with the same Guidances, we are providing a paper review copy.

The electronic files are contained on 1 CD-ROM using less than 1 MB. All electronic files have been scanned with Network Associates VirusScanNT Version 4.0.3a with Virus Definitions 4.0.4079. The electronic archive contains the following:

- Cover Letter
- FDA Form 356h
- Item 1 Table of Contents
- Item 8, Table of Contents
- Item 8, Notes to Reviewers
- Item 8, Quality of Life (Validation Report of QoL Instrument used in Studies 376-403 and 376- 404)

To facilitate quality assurance and flexibility in reviewing from electronic to paper versions, please note the following: 1) The paper review copy consists of 1 volume. 2) Volume is indicated on the binder label. 3) Page numbers will run consecutively and be located on the top right corner. 4) Item number designation is located on the lower right corner.

If you have any questions regarding this submission please contact me at 734/622-2346 or John Kirk at 734/622-7783, or send a facsimile to 734/622-3283.

Sincerely,

Joanna Hinton, Ph.D.
Senior Manager
Worldwide Regulatory Affairs

JH/kb 01-30-2001\RN-009\21-276\CI-0376\Letter
Attachments

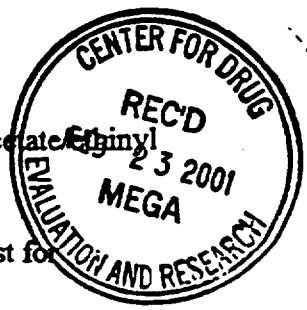
Desk Copy: Olga Cintron (HFD-540)
Iris Masucci, Pharm.D., (HFD-042)
Jennifer Mercier (HFD-580)

Pharmaceutical Research and Development
2800 Plymouth Road
Ann Arbor, MI
48105
Phone: (734) 622-7000

PARKE-DAVIS
A Warner-Lambert Division

BM

February 22, 2001



sNDA 21-276
Ref. No. 010
Estrostep® (norethindrone acetate/ethinyl estradiol) Tablets

Re: Response to FDA Request for Information

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products (HFD-540)
Document Control Room N214
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Wilkin:

Reference is made to our pending sNDA 21-276 for Estrostep®[a] (norethindrone acetate/ethinyl estradiol) tablets submitted on June 30, 2000 (Ref. No. 000) for the use of Estrostep in the treatment of moderate acne vulgaris. Reference is also made to a fax received on January 12, 2001, from Ms. Olga Cintron of your division that contained 3 questions from the Medical Officer. Reference is also made to an email received on January 17, 2001, from Ms. Cintron that contained a request to provide the control and data files for NONMEM for EE and N from studies 397 (healthy subjects) and 403 (patient population). This correspondence provides responses to these requests in electronic archive format.

Reference is also made to several other communications and agreements reached between Ms. Cintron and myself as detailed below:

Jan 17, 2001	Two e-mail exchanges between Ms. Cintron and myself to clarify acceptable format for providing response to FDA fax of Jan 12.
Jan 19, 2001	As requested by Ms. Cintron, a fax was sent providing the response to Question 1 on FDA fax of Jan 12, which was to clarify the report changes/corrections made in the December 20, 2000 amendment (Ref. No. 007).
Jan 19, 2001	A second fax was also sent to Ms. Cintron requesting review and agreement on 2 mock-up tables to answer the second and third questions from FDA fax of Jan 12.

ORIGINA

[a] Estrostep is a registered trademark of Warner-Lambert Company, its affiliates, and subsidiaries.

Jan 19, 2001	Ms. Cintron left me a voice mail message indicating she had received both of the faxes.
Jan 24, 2001	As requested, the NONMEM datasets and control files for 403 and 397 in ASCII format were emailed to Ms. Cintron.
Jan 25, 2001	In a telephone conversation between myself and Ms. Cintron, Ms. Cintron indicated she did not yet have a response on the acceptability of the mock tables that had been faxed to the Division on Jan 19 and she would follow-up. She also indicated she had received our email response to the Biopharm reviewer and had forwarded it appropriately. She requested we officially submit the email and contents to the NDA. I indicated that the data set for the 403 study was already provided in the original submission in accordance with the Electronic Submission guidance. After discussion, we agreed for administrative purposes that Parke-Davis would provide the study 397 pharmacokinetic data as a SAS transport file with the corresponding define.pdf file (Note: included in this submission).
Jan 31, 2001	As requested by Ms. Cintron in a telephone conversation, the 2 faxes from January 19 were combined and re-faxed to Ms. Cintron.
Feb 1, 2001	Ms. Cintron telephoned to respond to the faxes and our questions. She stated that the Division required no additional clarification on the weight corrections to the research reports although the details should be submitted officially for administrative purposes as electronic archive (Note: included in this submission). She also stated that we did not need to provide a response to the second and third questions of the FDA fax of January 12, which asked for additional clarification to response to Questions 4 and 7 provided in our December 20 amendment. She stated that the Medical Reviewer had everything he needed.

Cross-reference is also made to our submission of December 23, 1997, to NDA 20-130 (Ref. No. 38) to the Division of Reproductive and Urologic Drug Products, which included the final study report entitled "A Single- and Multiple-Dose Pharmacokinetic Study of Estrostep 1/20, 1/30, and 1/35 Tablets (Protocol 376-397)." That submission also contained an electronic copy of the final study report in WordPerfect Version 6.1 and ASCII files for the raw data for study 376-397 (pkdata_397.csv).

As requested, this submission thus contains the following:

- The response to Question 1 from the FDA Fax of January 12, 2001, that clarifies "the changes that were made (to the corrected reports) by each revised page in a distinguishable manner." This response is provided as a pdf file of the Parke-Davis' fax response sent on January 19, 2001. This is located in Item 8.

- Item 6 contains a Note to Reviewers which provides background on the 376-397 pharmacokinetic dataset and includes a copy of the email response sent on January 24, 2001 with the requested NONMEM datasets and control files for 376-403 and 376-397 in ASCII format.

- The NONMEM pharmacokinetic dataset for study 376-397 as SAS transport file with the corresponding define.pdf file. This is located in Item 11.

Additionally we are providing updated define.pdf files for Studies 403 and 404, located in Item 11, as we had indicated we would in our Response to Fax of October 25, 2000, Question 10, submitted on December 20, 2000 (Ref. No. 007). The updates made to the define.pdf are listed below:

- The decode for the value of .5 was added to the Codes column for the POP variable.
- Codes were added to the VISIT variable.
- In the LABS dataset, the decode for the value of 2 was added to the Codes column for the ABNML variable
- In the LABS dataset, the decode for the value of 0 was added to the Codes column for the CLINSIG variable.
- In the VITALS dataset, for the height, weight, blood pressure, and heart rate variables, when the Not Done box was checked (variables ending in '_NO'), the corresponding numeric field was filled in with 'N/D'.

As the SAS datasets for the 403 and 404 study are not included in this submission, links to the datasets from the define.pdf files are not provided. Similarly, as the annotated case report forms (CRFs) for all studies are not included in this submission, links to the annotated CRFs from the define.pdf files are not provided.

This response in its entirety is being provided in accordance with the January 1999 Guidances for Industry entitled, *Providing Regulatory Submissions in Electronic Format – NDAs* and *Providing Regulatory Submissions in Electronic Format – General Considerations*. The archival copy is provided in electronic format. All documents that require original signatures are provided as a paper archive copy. In accordance with the same Guidances, we are providing a paper review copy.

The electronic files are contained on 1 CD-ROM using approximately 1.9 MB. All electronic files have been scanned with Network Associates VirusScanNT Version 4.0.3a with Virus Definitions 4.0.4079. The electronic archive contains the following:

- Cover Letter
- FDA Form 356h
- Item 1 Table of Contents
- Item 6, Table of Contents
- Item 6, Notes to Reviewers
- Item 8, Table of Contents
- Item 8, Description of Report Corrections submitted Dec. 20, 2000
- Item 11, Table of Contents
- Item 11, Updated define.pdf for study 376-403
- Item 11, Updated define.pdf for study 376-404
- Item 11, PK dataset for 376-397 as SAS transport files and corresponding define.pdf

To facilitate quality assurance and flexibility in reviewing from electronic to paper versions, please note the following: 1) The paper review copy consists of 1 volume. 2) Volume is indicated on the binder label. 3) Page numbers will run consecutively and be located on the top right corner. 4) Item number designation is located on the lower right corner.

If you have any questions regarding this submission please contact me at 734/622-2346 or John Kirk at 734/622-7783, or send a facsimile to 734/622-3283.

Sincerely,

Joanna Hinton, Ph.D.
Senior Manager
Worldwide Regulatory Affairs

Desk Copy: Olga Cintron (HFD-540)

JH/kb
02-22-2001\RN-010\21-276\CI-0376\Letter

Attachments:
1 CD: Central Document Room
Volume 1: Item 1 Table of Contents, Item 6 Table of Contents, Item 6 Notes to Reviewers, Item 8 Table of Contents, Item 8 Description of Report Corrections submitted Dec. 20, 2000, and Item 11 Table of Contents, Updated define.pdf for study 376-403, Updated define.pdf for study 376-404, PK dataset for 376-397 as SAS transport files and corresponding define.pdf.

Pharmaceutical Research and Development
2800 Plymouth Road
Ann Arbor, MI
48105
Phone (734) 622-7000

PARKE-DAVIS
A Warner-Lambert Division

March 20, 2001

sNDA 21-276
Estrostep® (norethindrone acetate/ethinyl estradiol) Tablets

Re: Response to FDA Request for Information, Reviewer's Aid

NC

NEW CORRESP

Ms. Olga Cintron
Project Coordinator
Division of Dermatologic and Dental Drug Products (HFD-540)
Document Control Room N248
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Dear Ms. Cintron:

Reference is made to our pending sNDA 21-276 for Estrostep®[a] (norethindrone acetate/ethinyl estradiol) tablets submitted on June 30, 2000 (Ref. No. 000) for the use of Estrostep in the treatment of moderate acne vulgaris. Reference is also made to a telephone message received on March 16, 2001, from Ms. Olga Cintron of your division, requesting a Reviewer's Aid containing the Word version of Item 3 Annotated Prescribing Information.

This correspondence provides one diskette, containing the Word version of Item 3 Annotated Prescribing Information, as a Reviewer's Aid. The information provided on diskette is intended as a Reviewer's Aid and not as an Electronic Archive.

The electronic file is contained on 1 diskette using approximately 359 kb. This electronic file has been scanned with Network Associates VirusScanNT Version 4.0.3a with Virus Definitions 4.0.4125.

ORIGINAL

[a] Estrostep is a registered trademark of Warner-Lambert Company, its affiliates, and subsidiaries.

If you have any questions regarding this submission please contact me at 734/622-2346 or John Kirk at 734/622-7783, or send a facsimile to 734/622-3283.

Sincerely,

Clara Hooker

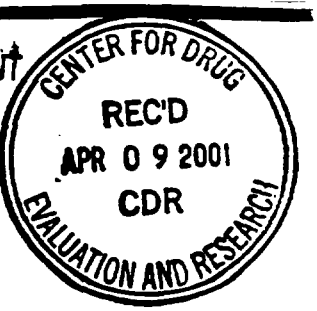
for \ Joanna Hinton, Ph.D.
Senior Manager
Regulatory Strategy and Registration
Worldwide Regulatory Affairs

JH\CH
03-20-2001\21-276\CI-0376\letter

Attachment (1 diskette)

Pharmaceutical Research
2500 Plymouth Road Phone: (734) 622-7000
Ann Arbor, MI
48105

ORIG AMENDMENT
BB



PARKE-DAVIS

April 6, 2001

sNDA 21-276
Ref. No. 011
Estrostep® (norethindrone acetate/ethinyl estradiol) Tablets

Re: Response to FDA Request for Information

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products (HFD-540)
Document Control Room N214
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Dear Dr. Wilkin:

Reference is made to our pending sNDA 21-276 for Estrostep®[a] (norethindrone acetate/ethinyl estradiol) tablets submitted on June 30, 2000 (Ref. No. 000) for the use of Estrostep in the treatment of moderate acne vulgaris.

Reference is also made to a phone conversation on March 15, 2001 between myself and Ms. Olga Cintron of your Division, Dr. Arzu Selen and Dr. Adebowale, both from the Division of Pharmaceutical Evaluation III, in which they requested specific raw pharmacokinetic data from studies 376-397 and 376-403 used to generate Figures 2 and 11 from Research Report 764-03375. Additionally, Ms. Cintron indicated this request could be responded to by email. As requested, the response to this request was made in an email I sent to Ms. Olga Cintron on March 16, 2001.

Reference is also made to a fax received on March 21, 2001 from Ms. Olga Cintron of the Division of Dermatologic and Dental Drug Products. The fax included a request for additional information from the Biopharm reviewer. Specifically, four requests for additional graphs and data analysis of the pharmacokinetic data from studies 376-397 and 376-403 were made. Additionally Ms. Cintron indicated this request could be responded to by email and followed with an official electronic archive submission. As requested, the response to this request was made in an email I sent to Ms. Olga Cintron on March 28, 2001.

[a] Estrostep is a registered trademark of Warner-Lambert Company, its affiliates, and subsidiaries.

ORIGINAL

This correspondence provides the two responses to the above two Biopharmaceutical requests in electronic archive format to ensure completeness of the sNDA 21-276 electronic archive.

This submission contains the following:

- Item 6 contains **Response to Phone Request of March 15, 2001**. This response includes the email sent on March 16, 2001 to Ms. Olga Cintron. In addition, we have included the three pdf files that were provided in the email.

- Item 6 also contains **Response to Fax Request of March 21, 2001**. This response includes the email sent on March 28, 2001 to Ms. Olga Cintron. In addition, we have included the pdf file that was attached in the email.

This response in its entirety is being provided in accordance with the January 1999 Guidances for Industry entitled, *Providing Regulatory Submissions in Electronic Format – NDAs* and *Providing Regulatory Submissions in Electronic Format – General Considerations*. The archival copy is provided in electronic format. All documents that require original signatures are provided as a paper archive copy. In accordance with the same Guidances, we are providing a paper review copy.

The electronic files are contained on one CD-ROM using approximately 990 kb. All electronic files have been scanned with Network Associates VirusScanNT Version 4.0.3a with Virus Definitions 4.0.4126. The electronic archive contains the following:

- Cover Letter
- FDA Form 356h
- Item 1 Table of Contents
- Item 6, Table of Contents
- Item 6, **Response to Phone Request of March 15, 2001**
- Item 6, **Response to Fax Request of March 21, 2001**

To facilitate quality assurance and flexibility in reviewing from electronic to paper versions, please note the following: 1) The paper review copy consists of one volume. 2) Volume is indicated on the binder label. 3) Page numbers will run consecutively and be located on the top right corner. 4) Item number designation is located on the lower right corner.

If you have any questions regarding this submission please contact me at 734/622-2346 or John Kirk at 734/622-7783, or send a facsimile to 734/622-3283.

Sincerely,

Joanna Hinton, Ph.D.
Senior Manager
Worldwide Regulatory Affairs

Desk Copy: Olga Cintron (HFD-540)

JH:kb
04-06-2001\RN-011\21-276\CI-0376\Letter
Attachments

Pharmaceutical Research and Development
2800 Plymouth Road
Ann Arbor, MI
48105
Phone: (734) 622-7000

PARKE-DAVIS
A Warner-Lambert Division

NDA ORIG AMENDMENT
N-000/BL

June 26, 2001

Apr 23/01
May 02/01
June 12/01
e-mails

NDA 21-276
Ref. No. 012
Estrostep® (norethindrone acetate/ethinyl estradiol) Tablets

RECEIVED
JUN 27 2001
CDR/CDER

NDA 20-130/S-007
Ref. No. 078
Estrostep 21/Fe Tablets

Re: Other: Proposed Additions to Pending Labeling

CENTER FOR DRUG
REC'D
JUN 28 2001
MEGA
EVALUATION AND RESEARCH

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental
Drug Products (HFD-540)
Document Control Room N214
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Susan Allen, M.D.
Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Document Control Room 17B-45
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Building
5600 Fishers Lane
Rockville, Maryland 20857

Dear Drs. Wilkin and Allen:

Reference is made to our pending sNDA 21-276 for Estrostep®[a] (norethindrone acetate/ethinyl estradiol) tablets submitted on June 30, 2000 (Ref. No. 000) to the Division of Dermatologic and Dental Drug Products (DDDDP) for the use of Estrostep in the treatment of moderate acne vulgaris.

ORIGINAL

[a] Estrostep is a registered product of Warner-Lambert Company, its affiliates and subsidiaries.

Reference is also made to Labeling Supplement 007 to NDA 20-130 (Ref. No 56) submitted on November 17, 2000, to the Division of Reproductive and Urologic Drug Products (DRUDP), for the use of Estrostep in the treatment of moderate acne vulgaris.

Reference is also made to several email exchanges between Ms. Olga Cintron of DDDDP and myself on April 27, 2001, May 2, 2001 and June 12, 2001. These email exchanges, per prior agreement, included proposed changes to pending labeling for Estrostep.

This correspondence is to provide you with official documentation of these email exchanges as previously agreed to.

For sNDA 21-276 held within the Division of Dermatologic and Dental Drug Products, we are providing this correspondence in accordance with the January 1999 Guidances for Industry entitled, *Providing Regulatory Submissions in Electronic Format – NDAs* and *Providing Regulatory Submissions in Electronic Format – General Considerations*. The archival copy is provided in electronic format. All documents that require original signatures are provided as a paper archive copy. In accordance with the same Guidances, we are providing a paper review copy which uses the archival PDF files, and not the Microsoft WORD .doc files.

For NDA 20-130/S-007 within the Division of Reproductive and Urologic Drug Products, we are providing this correspondence in its entirety as a paper review copy and as an exact duplicate of the sNDA 21-276 paper review copy for ease of review and to ensure consistency with the sNDA submission. Therefore, only copies of the original signed documents (356h and cover letter) will be provided to DRUDP.

This submission contains the following:

- Item 20: Other: Proposed Additions to Pending Labeling
  - E-mail of April 27, 2001, which includes cross-references to communications with both DDDDP and DRUDP and Parke-Davis's (a Division of Pfizer) counter-proposals to the Division's proposed labeling of April 23, 2001. Additionally included are the four e-mail attachments, two WORD documents (track2pfizer.doc and cleanpfizer2.doc) and the two associated pdf files.
  - E-mail of May 2, 2001, which includes cross-references to communications, cross-reference to the teleconference held on May 1, 2001 between FDA representatives from DDDDP, DRUDP, DDMAC and Parke-Davis colleagues, and summary of agreements and changes reached during the teleconference. Additionally, the two e-mail attachments, a WORD document (trackpfizer3.doc) and associated PDF file, for the labeling changes are included.

- E-mail of June 12, 2001, which includes cross-references to communications with both DDDDP and DRUDP, summary of changes to the labeling attachments, and four e-mail attached documents (two WORD: pfizerclean061201.doc and pfizer061201.doc and the two associated PDF files).

For the electronic submission, we are not including full book-marking and hypertext linking of the draft labeling, per our proposal in the email of June 12, 2001 since the labeling document still represents draft proposed labeling. Full book-marking and hypertext linking will be included once complete finalized agreements have been reached on the labeling. We are also providing a Table of Contents for Item 20 and it is called 'othertoc.pdf'.

The electronic files for sNDA 21-276 are contained on one CD-ROM using approximately 6.30 MB. All electronic files have been scanned with Network Associates VirusScanNT Version 4.0.3a with Virus Definitions 4.0.4142. The electronic archive contains the following:

- Cover Letter
- FDA Form 356h
- Item 1 Table of Contents
- Item 20, Table of Contents
- Item 20, Notes to Reviewers
- Item 20, E-mail of April 27, 2001 and attachments
- Item 20, E-mail of May 2, 2001 and attachments
- Item 20, E-mail of June 12, 2001 and attachments

To facilitate quality assurance and flexibility in reviewing from electronic to paper versions, please note the following: 1) The paper review copy consists of one volume. 2) Volume is indicated on the binder label. 3) Page numbers will run consecutively and be located on the top right corner. 4) Item number designation is located on the lower right corner.

If you have any questions regarding this submission, please feel free to contact me at 734/622-2346 or John Kirk at 734/622-7783 or send a facsimile to 734/622-3283.

Sincerely,

Joanna Hinton, Ph.D.
Senior Manager
Regulatory Strategy and Registration
Worldwide Regulatory Affairs

Desk Copy: Ms. Olga Cintron (HFD-540)
Ms. Jennifer Mercier (HFD-580)

JH/kb
06-26-2001\RN-012\21-276\RN-078\20-130\CI-0376\letter
Attachments